ADHD in Pediatric Epilepsy: Fact or Fiction?

ADHD in Childhood Epilepsy: Clinical Determinants of Severity and of the Response to Methylphenidate.

Rheims S, Herbillon V, Villeneuve N, Auvin S, Napuri S, Cances C, Berquin P, Castelneau P, Nguyen The Tich S, Villega F, Isnard H, Nabbout R, Gaillard S, Mercier C, Kassai B, Arzimanoglou A, the investigators of the Paediatric Epilepsy RN. *Epilepsia* 2016:57(7);1069–1077. doi: 10.1111/epi.13420.

OBJECTIVE: Attention-deficit/hyperactivity disorder (ADHD) is commonly observed in children with epilepsy. However, factors associated with the development of ADHD and which might help to guide its therapeutic management, remain an issue of debate. METHODS: We conducted a multicenter prospective observational study that included children, aged 6–16 years, with both epilepsy and ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. After inclusion, patients entered a 12–16 week follow-up period during which they were either treated with methylphenidate or they did not receive specific ADHD treatment. ADHD was evaluated with the ADHD Rating Scale-IV. RESULTS: One hundred sixty-seven patients were included, of which 91 were seizure-free during the preinclusion baseline period. At inclusion, the ADHD Rating Scale-IV total score was 30.4 ± (standard deviation) 9.2, the inattentive subscore was 17.3 ± 4.4, and the hyperactive subscore was 13.2 ± 6.6. We did not detect any difference of ADHD Rating Scale-IV scores across patients' age or gender, age at epilepsy onset, epilepsy syndrome, seizure frequency, or number of ongoing antiepileptic drugs. Methylphenidate was initiated in 61 patients, including 55 in whom a follow-up evaluation was available. At the last follow-up, 41 patients (75%) treated with methylphenidate and 39 (42%) of those who did not received ADHD therapy demonstrated ≥25% decrease of ADHD Rating Scale-IV total score ($p < 0.001$). Response to methylphenidate was greater in girls but was not influenced by any epilepsy-related variables. SIGNIFICANCE: We did not detect any epilepsy-related factor associated with the severity of ADHD. Twenty-five percent of patients did not respond to methylphenidate. A better understanding of the pathologic process that underlies ADHD development in childhood epilepsy might be required to improve therapeutic strategies.

Commentary

Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric comorbidity in epidemiologic and community studies of pediatric epilepsy. Rheims et al. are to be commended on conducting the first large-scale, multisite, albeit open, methylphenidate treatment study of ADHD in pediatric epilepsy. However, the time has come for the epilepsy community to give thought to theoretical and methodologic problems associated with this psychiatric comorbidity of pediatric epilepsy and determine what are facts and what is fiction.

From the theoretical perspectives, is the ADHD associated with epilepsy the same as the ADHD seen in those who do not have epilepsy? More specifically, do children with epilepsy with ADHD have primary attentional deficits or secondary deficits associated with slowing of processing speed (See review in (1)), subtle to severe cognitive impairments (1), and language-related learning disorders (2) are frequent in pediatric epilepsy. Epilepsy variables are not related to the inattentive type of ADHD (I-ADHD) found in youth with epilepsy who are of average intelligence (1). Early age of onset, poor seizure control, and number of antiseizure drugs, however, are reported in subjects with epilepsy and intellectual disability who also have high rates of the combined and hyperactive/impulsive types (H/I-ADHD) of ADHD (see review in [3]). The association of these epilepsy variables with low intelligence quotient (IQ), therefore, underscores the need to determine if the ADHD of epilepsy is secondary to the cognitive and linguistic deficits described earlier.

Despite evidence for the heritability of ADHD (4), no studies have investigated if ADHD and its attentional deficits are more frequent in the first-degree relatives of children with epilepsy who have ADHD than in the general population. The association of ADHD with lower IQ has genetic origins (5), which further emphasizes the importance of determining the role of low IQ in the attentional impairment of youth with epilepsy and ADHD.

From the methodologic perspective, four main problems plague studies of ADHD in epilepsy: 1) lack of diagnostic rigor and of large, representative, well-matched control groups of children with ADHD who do not have epilepsy; 2) heterogeneity of study samples; 3) potential iatrogenic effects of antiseizure drugs; and 4) rare assessment of the specific attentional impairments found in ADHD. A diagnosis of ADHD

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is made based on information from multiple informants (e.g., parents, teacher, child/adolescent); well-established tools, such as the ADHD Rating Scale –IV, the Swanson, Nolan, and Pelham Questionnaire; the Conners Brief Parent Rating Scale; the Strengths and Difficulties Questionnaire; and a structured psychiatric interview administered to the child and parent by a trained clinician. To achieve diagnostic reliability, the interviewer should be blind to the study's hypotheses. In addition, a second trained and blinded clinician should review at least 25% of the interviews to determine if there is diagnostic agreement. If there is disagreement about the diagnosis, a mechanism should be in place to reach a consensus diagnosis and determine if the child is or is not included in the study.

In terms of informants, with a few exceptions (6), most of the studies conducted to date have used only parent reports. They have not examined diagnostic reliability, interviewers have not been trained clinicians, and interviewers have not been blinded to the study's hypotheses. The Connecticut study demonstrated marked discrepancy between parent and youth reports on the Child Behavior Checklist 8 to 9 years after onset of epilepsy and 6 to 8 years later. Whereas parents reported problem behaviors in the youth with epilepsy but not in their siblings at baseline, there were no differences between the self-report scores for the children with epilepsy and siblings at both time points. Furthermore, structured interviews at the adult follow-up of this cohort did not find higher ADHD lifetime diagnoses in the subjects with epilepsy compared with their siblings.

Sole use of well-established ADHD questionnaires without conducting a differential diagnosis of psychiatric diagnoses is an additional problem. Parents, teachers, patients, and clinicians might misinterpret symptoms, such as agitation, irritability, and withdrawal, as hyperactivity and impaired attention, but most of the studies on ADHD in pediatric epilepsy have not examined if the hyperactivity and distractibility of the study subjects reflect diagnoses, such as anxiety disorders, depression, and psychosis, which can present with agitation, irritability, withdrawal, and distractibility. Youth with learning difficulties have difficulty paying attention and might be fidgety in the classroom environment. They are often misdiagnosed as having ADHD. Yet, although youth with epilepsy have subtle to severe cognitive and learning problems, learning disorders are not included in the differential diagnosis of ADHD in pediatric epilepsy.

Youth with intellectual disability have increased ADHD symptoms compared with the general population of children (7). The heterogeneity of study samples, due to inclusion of subjects with intellectual disability together with those with average intelligence, is a related important methodologic problem. However, heterogeneity does not appear to be a methodologic problem in studies of ADHD in large representative samples of children and adolescents with different epilepsy syndromes who have average intelligence (6, 8). These studies find higher ADHD rates in the subjects with epilepsy compared with typically developing children but no difference in ADHD diagnoses across syndromes.

In terms of antiseizure drugs, Glauser et al. (9) have demonstrated that valproate, compared with ethosuximide and lamotrigine, plays an important role in the attentional impairment of their large cohort of children with childhood absence epilepsy. Similar studies have not been conducted on a large sample of children with other epilepsy syndromes treated with one antiseizure drug. Such studies are essential to determine the role of antiseizure drugs in the ADHD of pediatric epilepsy.

Youth with ADHD who do not have epilepsy have impaired sustained attention and impulsivity evident on the Continuous Performance Task through errors of omission (impaired differentiation between target and nontarget stimuli or missed targets), errors of commission (incorrect response to nontarget stimuli), perseveration (anticipatory response), and variability of reaction time (response speed consistency). A few small-sample studies using the Continuous Performance Task identified errors of omission and slowing of response time in children with epilepsy with and without ADHD (10, 11) and errors of commission and perseveration in those with combined ADHD (12) and H/I-ADHD (11). Berl et al. (13) demonstrated impaired complex attention, but not simple attention, in a large sample localization-related pediatric epilepsy sample with IQ >70 compared with typically developing children. However, parent ADHD-IV ratings did not predict attentional deficits similar to the lack of association between the parent-reported Child Behavior Checklist attention score and the Confidence Index of the Continuous Performance Tests in the large multisite childhood absence treatment study.

What are the treatment implications of these issues? The multisite 12- to 16-week open study by Rheims et al. demonstrates that 75% of children with epilepsy and ADHD benefited from treatment with methylphenidate without a significant increase in seizure frequency. Yet, this study had the diagnostic problems previously mentioned. It used only a parent-completed ADHD Rating Scale–IV, the diagnosing and treating clinicians were not blinded, and the researchers did not conduct a differential diagnosis to rule out confounding psychiatric diagnoses. Furthermore, the study sample was heterogeneous and included children with a full-scale IQ that ranged from 59 to 150. The authors also did not specify how they decided to select 41 methylphenidate-treated and 39 untreated subjects with ADHD from among the 167 ADHD patients they recruited for the study.

From the research perspective, these theoretical and methodologic issues need to be addressed to determine if the ADHD of pediatric epilepsy is fact or fiction. In the era of evidence-based medicine, our field needs to move forward and conduct well-designed studies to determine if the inattention of children with epilepsy is, in fact, ADHD; if it is the same as the ADHD found in children without epilepsy, and how best to treat it.

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